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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,926	HESS ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending in the instant application and are examined herein.

Claim Objections

Claims 3, 5, and 9 are objected to because of the following informalities: there appears to be a typographical error in the phrase "encoding the native **for** of bradykinin B1" in each of the claims. It appears that the word "for" should be "form." Claims 4, 5, 6, 10, and 12 are objected to insofar as they depend from Claims 3, 5, and 9. Appropriate correction is required.

Claims 2-6 and 8-12 are objected to for their use of the indefinite article "a" in their recitation of "[a] non-human transgenic animal of claim X." Use of the definite article "the" would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse as claimed, does not reasonably provide enablement for animal species other than mice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enablement set forth above is not intended to suggest specific claim language, but rather is intended to advise Applicant of the broadest scope that is considered to be enabled. It is Applicant's responsibility to identify claim language that is properly supported in the specification and that falls within the scope acknowledged to be enabled. Proper support in the as-filed specification for any claim terminology introduced by amendment is always required.

Embryonic Stem Cell Technology is Limited to the Mouse. The specification fails to provide an enabling disclosure for the preparation of transgenic animals for species other than mice because the guidance offered in the specification is limited to the use of embryonic stem (ES) cells in the preparation of knock-in **mice** and no teachings or guidance are offered in regard to how one would have prepared any other type of transgenic mammal from embryonic stem cells. The specification contemplates the use of embryonic stem cells from any mammal in producing the claimed transgenic animal of the invention, for example, a non-human transgenic animal comprising a transgene encoding a human bradykinin B1 receptor and exhibiting a null phenotype for the native form of the bradykinin B1 receptor. The teachings of the specification, however, are limited to the use of embryonic stem cells in producing the claimed animals. The specification does not teach any other method for making a knockout or knock-in transgenic animal. Therefore, embryonic stem (ES) cell technology must be available to carry out the method needed to produce the claimed animals. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut (1997, Theriogenology 47: 63-72) provide a discussion of the methods for using ES cells to generate chimeras. Campbell and Wilmut acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline

transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. 1558, column 2, paragraph 1). Thus, ES cells are required for gene targeting experiments and the specification does not provide specific guidance for obtaining ES cells from any animal other than a mouse. Since ES cell technology is available only for mice and the claims encompass animals of any species, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals over the full scope and to produce transgenic animals for species other than mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 11, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 6 are indefinite in their recitation of the limitation that the the "human B1 bradykinin gene is operatively fused to the native bradykinin B1 receptor protein" because a gene cannot be operatively fused to a protein and therefore the claims are indefinite. Accordingly, the claims will not be further treated on the merits.

Claims 11 and 12 are indefinite in their recitation of "wherein the floxed gene has been excised." However, Claim 7, from which Claims 11 and 12 ultimately depend, requires that the animal must contain "a floxed marker gene." Since the limitations of the independent claim are necessarily incorporated into the dependent claims, Claims 11 and 12 likewise require the presence of "a floxed marker gene" with the further limitation "wherein the floxed gene has been excised." The animal cannot contain a floxed marker gene when the floxed gene has been excised. Thus, the limitation of the dependent claims

conflicts with the limitations of the independent claim (Claim 7). The claims are indefinite, cannot be interpreted, and will not be further treated on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pesquero et al. (2000, Proc. Natl. Acad. Sci. 97(14): 8140-8145), Hess et al. (1996, Immunopharmacology 33: 1-8), GenBank Accession No. BC034705 (July 2002), Menke et al. (1994, J. Biol. Chem. 269(34): 21583-21586), GenBank Accession No. NM_007539 (January 2002), Pesquero et al. (1996, Biochem. Biophys. Res. Comm. 220: 219-225), and Bonaventure et al. (1999, Molecular Pharmacology 56: 54-67).

The claims are directed to a non-human transgenic animal having a genome comprising at least one copy of a transgene encoding a human bradykinin B1 receptor protein, or a functional equivalent

thereof, and which exhibits a null phenotype for the native form of the bradykinin B1 receptor, such that the transgenic animal demonstrates a humanized B1 bradykinin receptor binding profile.

Pesquero et al. (2000) disclose a bradykinin B1 receptor knockout mouse. The mouse B1-receptor gene was cloned from a mouse genomic library and a targeting vector comprising a 1.0-kb genomic fragment 5' of the B1 coding region and a 7.0-kb genomic fragment 3' of the B1 coding region was constructed (page 8140, column 2, paragraph 2 and Figure 1A).

Hess et al. (1996) disclose that the agonist selectivity of the mouse B1 receptor differs significantly from the agonist selectivity of the human B1 receptor. The reference further discloses the isolation of a genomic clone encoding the mouse bradykinin B1 receptor.

GenBank Accession No. BC034705 (July 2002) discloses the cDNA sequence encoding the human bradykinin B1 receptor.

Menke et al. (1994) disclose the isolation of a cDNA clone encoding the human bradykinin B1 receptor using an expression cloning strategy.

GenBank Accession No. NM_007539 (January 2002) discloses the cDNA sequence encoding the mouse bradykinin B1 receptor.

Pesquero et al. (1996) disclose the cloning and functional characterization of the mouse bradykinin B1 gene. The gene encoding the mouse bradykinin B1 receptor was cloned from a mouse 129/SvJ genomic library by screening with a human B1 cDNA probe. The mouse bradykinin B1 receptor protein sequence is disclosed in Figure 1 and the cDNA sequence is disclosed in GenBank Accession No. NM_007539, as set forth above.

Bonaventure et al. (1999) disclose a knock-in mouse generated by replacing the coding region of the mouse 5-hydroxytryptamine $(5\text{-HT})_{1B}$ receptor gene with the coding region for the human 5-HT_{1B} receptor gene using homologous recombination in embryonic stem cells. The human coding sequence was thereby placed under control of the mouse 5-HT_{1B} receptor regulatory region and the expression

pattern for the human receptor in the transgenic mouse was identical to the expression pattern of the mouse receptor in a wild-type mouse. The mouse gene is said to be 'humanized' by replacement with the human gene.

In view of the disclosure of Hess et al. (1996) noting the pharmacological differences between the human and mouse bradykinin B1 receptors, one of skill in the art would have been motivated to produce a humanized system for *in vivo* analysis of the pharmacology of the human bradykinin B1 receptor. Thus, the skilled artisan would have been motivated to generate a mouse that does not express the mouse bradykinin B1 receptor, but which instead expresses the human form in its place. Since knock-in technology was well known and well developed in the art, as demonstrated by Bonaventure et al., it would have been obvious to one of skill in the art, at the time of the invention, to have made a knock-in mouse by replacing the coding sequence of the mouse bradykinin B1 receptor gene with the human bradykinin B1 receptor gene so that the human gene would be placed under control of the endogenous mouse bradykinin B1 receptor regulatory region (i.e., promoter and other elements). Placing the human gene under control of the mouse endogenous elements would ensure an appropriate pattern of expression and appropriate levels of expression of the human bradykinin B1 receptor in mouse tissues. The skilled artisan would have anticipated a reasonable expectation of success in generating the knock-in mouse because all the necessary genomic fragments and coding sequences were readily available in the prior art, as discussed above, such that only routine experimentation would be required to generate the requisite targeting constructs and produce a knock-in mouse using gene targeting techniques that are well known and well developed in the art.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pesquero et al. (2000, Proc. Natl. Acad. Sci. 97(14): 8140-8145), Hess et al. (1996, Immunopharmacology 33: 1-8), GenBank Accession No. BC034705 (July 2002), Menke et al. (1994, J. Biol. Chem. 269(34): 21583-21586), GenBank Accession No. NM_007539 (January 2002), Pesquero et al. (1996, Biochem. Biophys. Res. Comm. 220: 219-225), Bonaventure et al. (1999, Molecular Pharmacology 56: 54-67), and Milstone et al. (1999, Nucleic Acids Research 27(15): e10, i-iii).

Pesquero et al. (2000) disclose a bradykinin B1 receptor knockout mouse. The mouse B1-receptor gene was cloned from a mouse genomic library and a targeting vector comprising a 1.0-kb genomic fragment 5' of the B1 coding region and a 7.0-kb genomic fragment 3' of the B1 coding region was constructed (page 8140, column 2, paragraph 2 and Figure 1A).

Hess et al. (1996) disclose that the agonist selectivity of the mouse B1 receptor differs significantly from the agonist selectivity of the human B1 receptor. The reference further discloses the isolation of a genomic clone encoding the mouse bradykinin B1 receptor.

GenBank Accession No. BC034705 (July 2002) discloses the cDNA sequence encoding the human bradykinin B1 receptor.

Menke et al. (1994) disclose the isolation of a cDNA clone encoding the human bradykinin B1 receptor using an expression cloning strategy.

GenBank Accession No. NM_007539 (January 2002) discloses the cDNA sequence encoding the mouse bradykinin B1 receptor.

Pesquero et al. (1996) disclose the cloning and functional characterization of the mouse bradykinin B1 gene. The gene encoding the mouse bradykinin B1 receptor was cloned from a mouse 129/SvJ genomic library by screening with a human B1 cDNA probe. The mouse bradykinin B1 receptor protein sequence is disclosed in Figure 1 and the cDNA sequence is disclosed in GenBank Accession No. NM_007539, as set forth above.

Bonaventure et al. (1999) disclose a knock-in mouse generated by replacing the coding region of the mouse 5-hydroxytryptamine (5-HT)$_{1B}$ receptor gene with the coding region for the human 5-HT$_{1B}$ receptor gene using homologous recombination in embryonic stem cells. The human coding sequence was thereby placed under control of the mouse 5-HT$_{1B}$ receptor regulatory region and the expression pattern for the human receptor in the transgenic mouse was identical to the expression pattern of the mouse receptor in a wild-type mouse. The mouse gene is said to be 'humanized' by replacement with the human gene.

Milstone et al. (1999) disclose that retained selection markers can affect neighboring genes and alter phenotypes in transgenic mice (abstract and page 1, column 2, paragraph 2). The reference further discloses that these effects can be avoided by designing the targeting construct with loxP recombination sites flanking the marker gene (i.e., a floxed marker gene). The marker gene can then be excised from the mouse genome upon expression of Cre recombinase. The reference further discloses that removing selection markers after making one mutation allows for the use of the same selection marker in making additional mutations in the genome (abstract and page 1, column 1, paragraph 1).

In view of the disclosure of Hess et al. (1996) noting the pharmacological differences between the human and mouse bradykinin B1 receptors, one of skill in the art would have been motivated to produce a humanized system for *in vivo* analysis of the pharmacology of the human bradykinin B1 receptor. Thus, the skilled artisan would have been motivated to generate a mouse that does not express the mouse bradykinin B1 receptor, but which instead expresses the human form in its place. Since knock-in technology was well known and well developed in the art, as demonstrated by Bonaventure et al. (1999), it would have been obvious to one of skill in the art, at the time of the invention, to have made a knock-in mouse by replacing the coding sequence of the mouse bradykinin B1 receptor gene with the human bradykinin B1 receptor gene so that the human gene would be placed under control of the endogenous mouse bradykinin B1 receptor regulatory region (i.e., promoter and other elements). Placing the human

gene under control of the mouse endogenous elements would ensure an appropriate pattern of expression and appropriate levels of expression of the human bradykinin B1 receptor in mouse tissues. In view of the guidance of Milstone et al. (1999), the skilled artisan would have designed the targeting construct to include a floxed marker gene so that the selection marker could later be excised from the genome to avoid the effect on expression of neighboring genes and confounding phenotypes that accompany these undesired alterations in gene expression. The skilled artisan would have anticipated a reasonable expectation of success in generating the knock-in mouse because all the necessary genomic fragments and coding sequences were readily available in the prior art, as discussed above, such that only routine experimentation would be required to generate the requisite targeting constructs and produce a knock-in mouse using gene targeting techniques that are well known and well developed in the art.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632